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CLINICAL UTILITY GENE CARD UPDATE

Clinical utility gene card for: Ehlers–Danlos syndrome types I–VII and variants - update 2012

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Ehlers–Danlos syndrome (EDS) types I/II, III, IV, VI, VIIA/B, and VIIC[1]; or according to the Villefranche nosology[2]: classical type (EDS I and II), hypermobile type (EDS III), vascular type (EDS IV), kyphoscoliotic types (EDS VIA and VIB), arthrochalasic types (EDS VIIA and EDS VIIB), dermatosparactic type (EDS VIIC), unspecified types, and variants.[3–12]

1.2 OMIM# of the disease

130000, 130010, 130020, 606408, 130050, 225400, 229200, 614170, 601776, 614557, 130060, 225410, 225320, 612350, 130070.

1.3 Name of the analysed genes or DNA/chromosome segments

COL5A1, COL5A2, TNXB, COL3A1, PLOD1, ZNF469, PRDM5, CHST14, FKBP14, COL1A1, COL1A2, ADAMTS2, SLC39A13, B4GALT7

Disease	*Abbreviation*	*OMIM disease*	*Inheritance*	*Gene*	*OMIM gene*	*Chrom. location*
EDS, classical type	EDS type I/II	130000, 130010	AD	*COL5A1*	120215	9q34.2–q34.3
EDS, classical type	EDS type I/II	130000, 130010	AD	*COL5A2*	120190	9q34.2–q34.3
EDS, classical type	EDS type I	130000	AD	*COL1A1*	120150	17q21.33
EDS, hypermobile type	EDS type III	130020	AD	*TNXB*	600985	6p21.3
EDS due to Tenascin-X deficiency	EDS with TNXB deficiency	606408	AR	*TNXB*	600985	6p21.3
EDS, vascular type	EDS type IV	130050	AD	*COL3A1*	120180	2q31
EDS, kyphoskoliotic type	EDS type VIA	225400	AR	*PLOD1*	153454	1p36.22
EDS, kyphoskoliotic type	EDS type VIB	225400	AR	*ZNF469*	612078	16q24
Brittle Cornea syndrome 1	BCS 1	229200	AR	*ZNF469*	612078	16q24
Brittle Cornea syndrome 2	BCS 2	614170	AR	*PRDM5*	614161	4q27
EDS, musculo-contractural type; D4ST1-deficient EDS type	EDS type VIB	601776	AR	*CHST14*	608429	15q15.1
FKBP14-deficient EDS type	EDS type VIB	614557	AR	*FKBP14*	614505	7p15.1
EDS, arthrochalasic type	EDS type VIIA	130060	AD	*COL1A1*	120150	17q21.33

(Continued)

Disease	*Abbreviation*	*OMIM disease*	*Inheritance*	*Gene*	*OMIM gene*	*Chrom. location*
EDS, arthrochalasic type	EDS type VIIB	130060	AD	*COL1A2*	120160	7q22.1
EDS, cardiac valvular form	EDS with COL1A2 deficiency	225320	AR	*COL1A2*	120160	7q22.1
EDS, dermato-sparactic type	EDS type VIIC	225410	AR	*ADAMTS2*	604539	5qter
EDS, progeroid form	EDS with XGPT deficiency	130070	AR	*B4GALT7*	604327	5q35.2–q35.3
EDS, spondylocheiro dysplastic form	SCD-EDS	612350	AR	*SLC39A13*	608735	11p11.2

EDS VIB is not yet well defined. Some groups define EDS VIB as those clinically resembling EDS VIA with normal lysyl pyridinoline/hydroxylysyl pyridinoline (LP/HP) ratios. D4ST1-deficient EDS type, FKBP14-deficient EDS type, EDS spondylocheiro dysplastic form and Brittle Cornea syndrome 1 may be subsumed in this group.

1.4 OMIM# of the gene(s)

COL5A1 120215, *COL5A2* 120190, *TNXB* 600985, *COL3A1* 120180, *PLOD1* 153454, *ZNF469* 612078, *PRDM5* 614161, *CHST14 608429*, *FKBP14* 614505, *COL1A1* 120150, *COL1A2* 120160, *ADAMTS2* 604539, *SLC39A13* 608735, *B4GALT7* 604327.

1.5 Mutational spectrum

Missense mutations, nonsense mutations, splice site mutations, insertions, deletions, and genomic rearrangements.

Presently, more than 400 mutations are known for all 14 genes together. The majority of them (about 240) have been identified in the *COL3A1* gene.

1.6 Analytical methods

Genomic sequencing of coding regions, eventually MLPA (multiple ligation dependent analysis) or array CGH for detection of genomic rearrangements and large deletions.

1.7 Analytical validation

Direct sequencing of both DNA strands; verification of sequence, MLPA and array CGH results with a second DNA extraction and a second PCR or hybridisation, respectively.

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1.8 Estimated frequency of the disease
(incidence at birth ('birth prevalence') or population prevalence)
The prevalence is estimated between 1:5000 and 1:100 000 depending on the EDS type.[1,2]

The autosomal recessively inherited EDS types are much rarer compared to the dominantly inherited EDS types.

1.9 If applicable, prevalence in the ethnic group of investigated person
Not applicable for most EDS types except for EDS type VIA, which is most prevalent in the Middle East.

1.10 Diagnostic setting

	Yes	No
A. (Differential) diagnostics	☒	☐
B. Predictive testing	☒	☐
C. Risk assessment in relatives	☒	☐
D. Prenatal	☒	☐

Comment: Prenatal diagnosis is rarely requested for EDS.

2. TEST CHARACTERISTICS

	Genotype or disease		A: True positives B: False positives	C: False negative D: True negative
	Present	Absent		
Test				
Positive	A	B	Sensitivity:	A/(A + C)
			Specificity:	D/(D + B)
Negative	C	D	Positive predictive value:	A/(A + B)
			Negative predictive value:	D/(C + D)

2.1 Analytical sensitivity
(proportion of positive tests if the genotype is present)
The analytical sensitivity should be nearly 100%, if a deletion/duplication diagnostic test has been made for genes with the possibility of a genomic rearrangement. However, regulatory mutations in non-coding regions are supposed to be missed with exon scanning techniques, even if these types of mutations have not yet been reported in EDS.

2.2 Analytical specificity
(proportion of negative tests if the genotype is not present)
Analytical specificity is nearly 100% because false positives may at the most arise due to misinterpretation of rare polymorphic variants.

2.3 Clinical sensitivity
(proportion of positive tests if the disease is present)
The clinical sensitivity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if only a quantification can be made case by case.

Clinical sensitivity is highly dependent on the EDS type based on fulfilment of the clinical criteria as well as of the biochemical and ultrastructural dermal findings documented in the Villefranche nosology:[1,2]

- It is 50–90% for EDS type I/II (*COL5A1* and *COL5A2* gene),[3,4] which is genetically heterogeneous with additional, still unknown gene loci.
- It is 95% for EDS type IV (*COL3A1* gene),[6] *EDS* types VIIA and VIIB (*COL1A1* and *COL1A* gene, respectively) and EDS type VIA (*PLOD1* gene).[7]
- Sensitivity is not known in the recessively inherited clinical entities including Brittle Cornea syndrome 1 and 2 (*ZNF469* and *PRDM5* gene),[11] D4ST1-deficient EDS (*CHST14* gene),[8] FKBP14-deficient EDS,[12] dermatosparactic type *(ADAMTS2* gene),[9] EDS progeroid form (*B4GALT7* gene) and EDS spondylocheiro dysplastic form (*SLC39A13* gene).[10]

2.4 Clinical specificity
(proportion of negative tests if the disease is not present)
The clinical specificity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if only a quantification can be made case by case.

Clinical specificity is nearly 100%.

2.5 Positive clinical predictive value
(life time risk to develop the disease if the test is positive)
As all EDS types are fully penetrant, the positive clinical predictive value is 100%. However, depending on EDS type, there may be highly variable clinical expressivity.

2.6 Negative clinical predictive value
(probability not to develop the disease if the test is negative)
Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested: Nearly 100%.

Index case in that family had not been tested: Five to ninty-five percent, corresponding to the detection rate in the genes of the different EDS types. This question arises quite often in EDS type IV if the index patient has died already.

3. CLINICAL UTILITY

3.1 (Differential) diagnosis: The tested person is clinically affected
(To be answered if in 1.10 'A' was marked)

3.1.1 Can a diagnosis be made other than through a genetic test?

No	☐ (continue with 3.1.4)	
Yes	☒	
	Clinically	☒
	Imaging	☐
	Endoscopy	☐
	Biochemistry	☒
	Electrophysiology	☐
	Other (please describe)	Ultrastructural analysis of dermis
	Biochemically	Collagen electrophoresis (electrophoretic mobility of collagen chains from cell culture), analysis of urinary pyridinolines (abnormal ratio of LP and HP cross-links)

EDS type	*Clinical*	*Ultrastructural analysis*	*Collagen electrophoresis*	*Urinary LP/HP*
I/II	+ +	+ +	(+)	−
III	+	−	−	−
IV	+ +	(+)	+	−
VIA	+ + +	+	+ +	+ + +
VIB	+ + +	+	−	−
VIIA	+ + +	+ +	+	−
VIIB	+ +	+	+ + +	−
VIIC	+ + +	+ + +	+ + +	−

As EDS comprises a group of different entities, each with highly variable clinical expressivity, a primary molecular genetic analysis for differential diagnostics is indicated only in exceptional cases with classical clinical features and known associated mutations. Histological/ultrastructural and biochemical/biophysical investigations should be performed initially, if ever possible. The significance of different collagen diagnostic approaches in different EDS types is illustrated in the table. Comparing EDS type VIIA and VIIB, there is a marked difference in clinical severity and in ultrastructural changes with more serious effects in EDS type VIIA. Conversely, pN-alpha1(I)-chains are more difficult to detect than pN-alpha2(I)-chains following collagen electrophoresis.

3.1.2 Describe the burden of alternative diagnostic methods to the patient

Initial clinical, biochemical, and ultrastructural investigations complement the molecular genetic analysis which, however, cannot replace the former. As ultrastructural analysis and collagen electrophoresis require a preceding skin biopsy, refusal of the patient towards this more invasive intervention compared with drawing a blood sample has to be respected.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?

Unknown.

3.1.4 Will disease management be influenced by the result of a genetic test?

No	☐	
Yes	☒	
	Therapy (please describe)	As a causal therapy is not possible, all efforts centre on management. Treatment with the β-blocker Celiprolol was shown in a randomized study to be associated with a decrease in arterial rupture in vascular EDS patients and might be the treatment of choice for physicians aiming to prevent major complications in patients with vascular EDS.[13,14]
	Prognosis (please describe)	The genetic diagnosis essentially contributes to classification of cases with indistinct clinical, biochemical, or ultrastructural features. This is the basis for prognostic statements and genetic counselling.
	Management (please describe)	Specific supportive therapy of joints and musculature in patients with EDS type I/II, III, VI, and VIIA/B by isotonic training at home after physiotherapeutic instructions and under regular controls. After surgical interventions, wounds should be closed without tension, preferably in two layers; deep stitches should be applied generously and cutaneous sutures left in place for twice as long as usual. Regular follow-up/ control of the aorta and the large arteries regarding dilatation, aneurysm formation, or dissection by ultrasound or MRI – the regular intervals depend on the dynamic of the vascular changes. Pregnancy is dangerous for the patient with EDS type IV and for her child because of tissue fragility leading to rupture of the uterus or the arteries before delivery – rupture of the arteries might occur also days post partum; hence, delivery has to be planned in advance and has to occur in a centre; C-section seems not to be a method to decrease such complications. Ophthalmologic evaluation in EDS type VI and Brittle cornea syndrome. Early orthopaedic and surgical measures in EDS types VIIA/B.

3.2 Predictive setting: The tested person is clinically unaffected but carries an increased risk based on family history

(To be answered if in 1.10 'B' was marked)

3.2.1 Will the result of a genetic test influence lifestyle and prevention?

Yes. If the test result is positive (please describe)

Frequent interdisciplinary follow-up, depending on EDS type (see above).

- Specific therapeutic support of joints and musculature.
- Sport: avoid competitive and contact sport activities in EDS types with predominant involvement of joints.
- Protection of legs, arms, and face with athletes' pads or bandages against traumatic skin injuries leading to ugly scars.
- Scrutiny for eventually developing aneurysms, special caution during surgery, tight follow-up of pregnancy.
- Emergency health card noting information about the diagnosis, possible complications, and therapeutic measures; especially in EDS types with vascular involvement.
- Wound protection in EDS types with involvement of skin and a tendency to haematomas.
- When skin tears do occur, irregularly frayed wound margins should be excised and precisely adapted to allow (rapid) healing without dystrophic scarring, which is especially important in the case of facial wounds; numerous fine, atraumatic stitches should be used and left in place for twice as long as usual.

If the test result is negative (please describe)

Follow-up is required in a clinically affected person, if the disease causing mutation could not be identified. In contrast, follow-up is dispensable in a family member, if a familial mutation has been excluded.

3.2.2 Which options in view of lifestyle and prevention does a person at-risk have if no genetic test has been done (please describe)?

Interdisciplinary follow-up considering all possible EDS types if the index patient had not been analysed genetically.

Regular and specific follow-up if the index patient's EDS type is known.

3.3 Genetic risk assessment in family members of a diseased person

(To be answered if in 1.10 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?

Yes.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?

No. A positive genetic test in the index patient supersedes the need to search for further genetic causes but gives the opportunity for targeted mutation analysis in further affected family members.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?

Yes. Owing to clinical variability within one family and limited presentation of full clinical features at birth or in early childhood genetic testing enables early diagnosis and intervention.

3.4 Prenatal diagnosis

(To be answered if in 1.10 'D' was marked)

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnostic?
Yes.

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe)

In many cases, the genetic diagnostics contribute substantially to the classification of EDS type, if clinical, biochemical, and ultrastructural findings are not fully informative. Recognising clinical symptoms as belonging to the EDS and classifying them as a given EDS type is prerequisite for clinical prognosis, specific therapy, and official acceptance as severe handicap. Genetic testing gives insight to inheritance pattern and allows reasonable genetic counselling. In children with a tendency to haematomas, a suspicion of child abuse may be alleviated through the correct diagnosis of EDS type. The correct diagnosis will end a diagnostic odyssey and the unwarranted suspicion of hypochondria, and the appropriate patient organisation can now be approached.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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